Increased Long-Term Cardiovascular Risk After Total Hip Arthroplasty: A Nationwide Cohort Study

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Increased Long-Term Cardiovascular Risk After Total Hip Arthroplasty

A Nationwide Cohort Study

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Abstract: Total hip arthroplasty is a common and important treatment for osteoarthritis patients. Long-term cardiovascular effects elicited by osteoarthritis or the implant itself remain unknown. The purpose of the present study was to determine if there is an increased risk of late cardiovascular mortality and morbidity after total hip arthroplasty surgery.

A nationwide matched cohort study with data on 91,527 osteoarthritis patients operated on, obtained from the Swedish Hip Arthroplasty Register. A control cohort (n = 270,688) from the general Swedish population was matched 1:3 to each case by sex, age, and residence. Mean follow-up time was 10 years (range, 7–21).

The exposure was presence of a hip replacement for more than 5 years. The primary outcome was cardiovascular mortality after 5 years. Secondary outcomes were total mortality and re-admissions due to cardiovascular events.

During the first 5 to 9 years, the arthroplasty cohort had a lower cardiovascular mortality risk compared with the control cohort. However, the risk in the arthroplasty cohort increased over time and was higher than in controls after 8.8 years (95% confidence interval [CI] 7.0–10.5). Between 9 and 13 years postoperatively, the hazard ratio was 1.11 (95% CI 1.05–1.17). Arthroplasty patients were also more frequently admitted to hospital for cardiovascular reasons compared with controls, with a rate ratio of 1.08 (95% CI 1.06–1.11).

Patients with surgically treated osteoarthritis of the hip have an increased risk of cardiovascular morbidity and mortality many years after the operation when compared with controls.

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Abbreviations: CDR = Cause of Death Register, CI = confidence interval, HR = hazard ratio, NPR = Swedish National Patient Register, NSAID = nonsteroidal anti-inflammatory drugs, OPG = osteoprotegerin, RANKL = receptor activator of nuclear factor κ B ligand, RANKL = receptor activator of nuclear factor κ B ligand, RR = rate ratio, SHAR = Swedish Hip Arthroplasty Register.

INTRODUCTION

The pathogenesis of cardiovascular disease is causally related to inflammatory processes.[1–3] Conditions associated with inflammatory activity such as rheumatoid arthritis[4,5] or poor dental health[6,7] increase the risk of cardiovascular events.[4,8] Parallel with these insights, primary osteoarthritis has moved from being perceived as a wear-and-tear condition to an inflammatory disease.[9] Moreover, the most common treatment modality for symptomatic osteoarthritis is joint replacement, a surgical procedure that by itself induces inflammation.[10] It is unknown how osteoarthritis and its surgical treatment impact the cardiovascular system.

Worldwide more than 1 million patients receive a total hip arthroplasty for osteoarthritis every year[11] and, compared with other common joint replacements, it is associated with a high incidence of long-term inflammatory foreign-body tissue reactions.[12,13] In the early phase after total hip arthroplasty surgery, mortality is increased when compared with the general population,[14] but this is later followed by a reduced mortality in arthroplasty patients.[15–17] The longest hitherto published follow-up of mortality after total hip arthroplasty is for <13 years, but long-term cardiovascular mortality and morbidity have not been investigated beyond this period.

The aim of this study was to determine if there is a late correlation between total hip arthroplasty and cardiovascular events. We hypothesized that total hip arthroplasty patients more than 5 years after index recorded surgery have an increased risk for cardiovascular morbidity and mortality compared with the general population.

METHODS

Design and Setting

We conducted a nationwide, matched, cohort study. During the study period from 1992 to 2005, the average Swedish

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The study complied with the Declaration of Helsinki and the protocol was approved by the Stockholm local ethics committee (dnr 2012/1163-31/1). Informed consent was waived according to practice in Sweden since no individual patient can be identified in the large, population-based cohort used for analysis.
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population was 8.9 million residents and a total of 256,298 total hip arthroplasties were performed.[18,19] Follow-up data on deaths, causes of death, admissions to inpatient care, and reasons for inpatient care, were collected until 2012.

Study Population

Cases

The arthroplasty cohort was recruited from the Swedish Hip Arthroplasty Register (SHAR).[19] We included only patients operated on due to primary osteoarthritis with a cemented total hip arthroplasty and excluded rare implants occurring <300 times in the SHAR. This was done to decrease surgeon selection bias from implant fixation (cemented vs uncemented) and bias from underlying hip diagnosis (primary or post-traumatic osteoarthritis or pediatric hip diseases) on mortality.

Controls

Each case was matched with 3 random controls that were not present in the SHAR through Statistics Sweden's registry of the total population. These were matched to the arthroplasty cohort by sex, age ±5 years, and residence. Residence was defined as municipality, except for the 3 largest cities (Stockholm, Malmö, and Gothenburg) where the municipality was subdivided into parishes. The matching criteria were chosen in order to limit socioeconomic confounding. All register data were matched with their unique Swedish personal identity numbers.

Data Sources

The cohorts were recruited from SHAR and Statistics Sweden. The SHAR was founded in 1979 and provides prospective observational nationwide data on hip arthroplasties. Since 1992, personal identity numbers have been collected, allowing for a patient-specific follow-up with a coverage of 97%.[19] The registry is the second oldest arthroplasty quality register in the world and captures 98% of all patients operated on with a hip arthroplasty from all Swedish hospitals. Statistics Sweden's registry of the total population started in 1968 and includes detailed information on all individuals' baseline demographics and places of residence.

The outcomes were identified from the Swedish National Patient Register (NPR) and the Cause of Death Register (CDR). The NPR was started in 1964 and includes all inpatient care in Sweden since 1987 with discharge codes according to ICD-9 and ICD-10 together with admission and discharge dates. The proportion of patients with a given diagnosis where the registry code is deemed correct (positive predictive value) is estimated around 85% to 90%.[20] The CDR includes the supposed underlying cause of death among Swedish citizens since 1961 and has a completeness of 100%.

Variables

Exposure was defined by the presence of a total hip arthroplasty. Apart from the matched age, sex, and residence, we also adjusted for comorbidity calculated by cross-matching with the NPR. ICD codes from admissions 2 years prior to surgery, not including the surgery admission, were used in order to estimate Charlson co-morbidity index. Apart from adjusting for the index, we also adjusted separately for myocardial infarction, chronic heart failure, cerebrovascular disease, diabetes mellitus, renal disease, and chronic obstructive pulmonary disease. Adjustment for smoking was not possible, but we used death due to lung cancer as a way to compare smoking prevalence between the cases and controls as it highly correlates with smoking. Furthermore, those with dementia, malignancies, or hemiplegia were excluded from the models as these conditions would most likely be more severe among the controls due to selection bias.

Outcome

The primary outcome was death due to cardiovascular disease as defined by the underlying main cause of death (see Supplementary Code Table, http://links.lww.com/MD/A687). Secondary outcomes were overall death, cardio-specific deaths, cerebral-specific deaths, and hospital admissions due to cardiovascular disease.

The start date for each case in the study was the surgery date, while the controls were assigned to the corresponding case's date of surgery. For arthroplasty patients occurring twice due to bilateral surgery, the first surgery date was chosen. End of follow-up was defined as death or being alive on December 31, 2012. The minimum follow-up time was 5 years. For the admission outcome, we included all admissions with a discharge date 5 years or more after the start date, and prior to the date of death. Admissions during which a patient died were excluded in order to avoid reporting twice on the same outcome.

Statistical Analyses

We used the Cox proportional hazards regression for death outcomes. The proportional hazards assumption was tested using Grambsch and Therneau's proposed test. We found a violation for the exposure variable, Charlson Comorbidity Index, and sex. We therefore stratified for the latter 2, while the exposure variable was modeled through time-splits. Two different approaches were chosen: The time was split into periods of 5 years, and then each period was separately modeled; the time was split into periods of 6 months and a single model was fitted with an interaction term between the exposure and the start-time for each split. Because the time was divided into several splits, a patient can occur several times but only the last period will contain the outcome event. For example, a patient that died after 15 months will occur thrice; 0 to 6, 6 to 12, and 12 to 15 months, but only the last period will contain the event indicator (i.e., death). Since the start time within each split is independent of the event status, it can be used as an interaction term. In order to ascertain that increased mortality was not due to reoperations, we censored cases in the arthroplasty group and their corresponding controls at the time of reoperation in a supplementary analysis.

The number of admissions was modeled using negative binomial regression. The regression is similar to Poisson regression, with the main exception that it allows for over-dispersion; in other words, the mean does not have to be equal to the variance, by estimating an additional parameter. Each regression model contained time as an offset term permitting the coefficients to be interpreted as rate ratios (RRs) instead of counts.

All continuous variables were tested for nonlinearity. If nonlinearity was indicated by a likelihood ratio-test resulting in a P value below 0.05, the variable was modeled with a restricted cubic spline. To avoid overfitting the regression model by choosing too many knots, the number of spline knots was chosen using the Bayesian information criterion.

All analyses were performed using R 3.2.2, using the rms-package (v. 4.3-1) for survival modeling, using the MASS-package (v. 7.3-44) for negative binomial regression.

RESULTS

Study Participants

For the 362,215 participants in the study (91,527 arthroplasty group/270,688 control group) the mean age at start date was 71 years and 58% were females (Table 1). The differences between cases and controls were mostly negligible regarding baseline demographics, although comorbidities and death due to lung cancer were more frequent among the controls. The overall mortality rate was 48% during the study; of these, 16% had died due to cardiovascular causes (Table 2). The longest follow-up time was 21 years; the interquartile range for the follow-up was 7 to 13 years.

Cardiovascular Mortality

The arthroplasty group exhibited a lower risk for cardiovascular mortality during the first 5 to 9 years, hazard ratio (HR) 0.94, 95% confidence interval (CI) 0.89 to 0.98. Thereafter, the risk increased and between 9 and 13 years postoperatively, HR was 1.11 (95% CI 1.05–1.16), where it remained elevated during the remaining study period (Table 3, Figure 1). When the time interaction was modeled using a spline, the cross-over occurred after 8.8 years (95% CI 7.0–10.5) for cardiovascular mortality and after 8.8 years (95% CI 8.3–9.3) for overall mortality (Figure 1). Censoring at reoperation did not change the mortality estimates (see Supplement, http://links.lww.com/MD/A687).

TABLE 1. Study Population Characteristics

Variable	Control Group (N = 300,414)	Arthroplasty Group (N = 91,973)
Age	71.1 (±8.9)	70.6 (±8.9)
Female	174,334 (58.0%)	53,326 (58.0%)
Comorbidity		
Cardiovascular		
Cerebrovascular disease	6533 (2.2%)	1404 (1.5%)
Myocardial infarction	4043 (1.3%)	949 (1.0%)
Heart failure	3299 (1.1%)	761 (0.8%)
Other		
Peripheral vascular disease	1502 (0.5%)	300 (0.3%)
Malignancy*	5722 (1.9%)	1627 (1.8%)
Metastasis*	183 (0.1%)	45 (0.0%)
Chronic pulmonary disease	2211 (0.7%)	444 (0.5%)
Dementia	1049 (0.3%)	66 (0.1%)
Peptic ulcer	1005 (0.3%)	582 (0.6%)
Rheumatic disease	748 (0.2%)	378 (0.4%)
Diabetes uncomplicated	704 (0.2%)	167 (0.2%)
Diabetes complicated	394 (0.1%)	49 (0.1%)
Renal disease	302 (0.1%)	94 (0.1%)
Mild liver disease	147 (0.0%)	49 (0.1%)
Severe liver disease	30 (0.0%)	8 (0.0%)
Paraplegia*	47 (0.0%)	11 (0.0%)
Obesity†	37 (0.0%)	26 (0.0%)
Psychoses†	1105 (0.4%)	143 (0.2%)
Alcohol†	821 (0.3%)	222 (0.2%)
Charlson index		
None	287,214 (95.6%)	88,640 (96.4%)
1–2	12,511 (4.2%)	3209 (3.5%)
≥3	689 (0.2%)	124 (0.1%)
Mean (SD)	0.08 (±0.43)	0.07 (±0.38)

Continuous variables are presented with mean and standard deviation.
SD = standard deviation.
* Excluded from the regression models.
† Calculated 5 y prior to surgery using the Elixhauser comorbidity groups.

TABLE 2. Outcomes

Variable	Control Group (N = 300,414)	Arthroplasty Group (N = 91,973)
Mortality outcomes		
Overall deaths due to cardiovascular disease	23,169 (7.7%)	7100 (7.7%)
>5 y	15,167 (6.0%)	5152 (6.3%)
>10 y	6318 (4.4%)	2304 (4.9%)
>15 y	1537 (3.3%)	561 (3.6%)
All deaths	142,809 (47.5%)	42,022 (45.7%)
>5 y	93,861 (37.3%)	31,408 (38.6%)
>10 y	41,586 (29.2%)	15,198 (32.0%)
>15 y	10,801 (22.9%)	4082 (25.8%)
Lung cancer deaths	4060 (1.4%)	1054 (1.1%)
Admissions (≥5 y)		
Number of cardiovascular admissions		
None	265,703 (88.4%)	79,467 (86.4%)
1–2	27,811 (9.3%)	9852 (10.7%)
≥3	6900 (2.3%)	2654 (2.9%)
Number of cardiac admissions		
None	279,070 (92.9%)	84,321 (91.7%)
1–2	16,476 (5.5%)	5820 (6.3%)
≥3	4868 (1.6%)	1832 (2.0%)
Number of cerebral admissions		
None	284,324 (94.6%)	86,102 (93.6%)
1–2	14,655 (4.9%)	5259 (5.7%)
≥3	1435 (0.5%)	612 (0.7%)

Admissions for Cardiovascular Events

The numbers of admissions to inpatient care were unevenly distributed between controls and cases, with arthroplasty patients being slightly more frequently admitted to hospital for any cardiovascular reason than control individuals (13.6% vs 12.0%, see Table 2). The most common reason for a cardiovascular admission was a cardiac event, with 6.3% of all arthroplasty patients admitted once or twice for cardiac events as compared with 5.6% of all control individuals. Similarly, a higher proportion of arthroplasty patients were admitted to inpatient care more than twice due to cardiac events (2.0%) when compared with control individuals (1.8%).

The adjusted risk of any admission to inpatient care due to any cardiovascular reason was slightly higher for patients operated on with a hip arthroplasty when compared with controls (RR 1.08; 95% CI 1.06–1.11). Within the most common subcategory of cardiovascular admissions, cardiac admissions, the adjusted RR was 1.06 (95% CI 1.03–1.10) for arthroplasty patients when compared with controls (Table 4).

TABLE 3. Crude and Adjusted Estimates for the Full Period and 4 y Subperiods

			Crude		Adjusted	
Variable	**Total**	**Event**	**HR**	**2.5% to 97.5%**	**HR**	**2.5% to 97.5%**
Cardiovascular mortality						
Period: 5.0–8.9 y						
Control	247,870	7307 (3.0%)	1	Ref	1	Ref
Arthroplasty	80,212	2288 (2.9%)	0.95	0.91–1.00	0.94	0.89–0.98
Period: 9.0–12.9 y						
Control	166,826	4653 (2.8%)	1	Ref	1	Ref
Arthroplasty	55,421	1737 (3.1%)	1.12	1.06–1.18	1.10	1.04–1.16
Period: 13.0–16.9 y						
Control	76,693	2347 (3.1%)	1	Ref	1	Ref
Arthroplasty	25,594	841 (3.3%)	1.08	1.00–1.17	1.07	0.99–1.16
Period: 17.0–21.0 y						
Control	24,888	631 (2.5%)	1	Ref	1	Ref
Arthroplasty	8180	222 (2.7%)	1.07	0.92–1.25	1.10	0.94–1.28
Overall: 5.0–21.0 y						
Control	247,870	14,938 (6.0%)	1	Ref	1	Ref
Arthroplasty	80,212	5088 (6.3%)	1.03	1.00–1.06	1.02	0.98–1.05
Overall mortality						
Period: 5.0–8.9 y						
Control	247,870	42,126 (17.0%)	1	Ref	1	Ref
Arthroplasty	80,212	12,684 (15.8%)	0.92	0.90–0.94	0.90	0.88–0.92
Period: 9.0–12.9 y						
Control	166,826	29,769 (17.8%)	1	Ref	1	Ref
Arthroplasty	55,421	10,670 (19.3%)	1.07	1.05–1.10	1.05	1.03–1.08
Period: 13.0–16.9 y						
Control	76,693	15,502 (20.2%)	1	Ref	1	Ref
Arthroplasty	25,594	5735 (22.4%)	1.11	1.08–1.14	1.11	1.07–1.14
Period: 17.0–21.0 y						
Control	24,888	4498 (18.1%)	1	Ref	1	Ref
Arthroplasty	8180	1725 (21.1%)	1.16	1.10–1.23	1.19	1.13–1.26
Overall: 5.0–21.0 y						
Control	247,870	91,895 (37.1%)	1	Ref	1	Ref
Arthroplasty	80,212	30,814 (38.4%)	1.01	1.00–1.02	1.00	0.99–1.01

At each subperiod those who have not experienced an event by the end are marked as alive at the end of the period. The adjusted HR contains all variables as previously stated in the statistics section.
HR = hazard ratio.

Censoring at reoperation did not change the risk estimates (see Supplement, http://links.lww.com/MD/A687).

DISCUSSION

In our nationwide cohort study of patients with surgically treated osteoarthritis of the hip, we found an increased long-term mortality and morbidity compared with controls. This effect was mainly attributable to an increased risk of cardiovascular disease and an increased risk of admissions to hospital care due to cardiovascular events. Our findings indicate an association of surgically treated hip osteoarthritis with diseases of the cardiovascular system, an association that—at least to our knowledge—has not been described before. Hip arthroplasty has, however, been associated to peripheral arterial disease at long-term follow up.[21] This study was performed in China which implies that the association between total hip arthroplasty and vascular disease may be generalized to different regions of the world. The generalizability of the results on a global scale is further supported by the fact that the Swedish hip arthroplasty cohort differs marginally when compared with other large joint arthroplasty cohorts in the Nordic countries[22–24] as well as in England,[25] Australia,[26] New Zeeland,[27] and United States.[28] While the type of implants may differ between countries, many have higher re-operation rates than Sweden, and there is little reason to believe that the cardiovascular effect would be smaller in poorer performing implants.

The increased number of hospital admissions for arthroplasty patients due to cardiovascular reasons indicates an increased overall cardiovascular morbidity for these individuals. Both crude numbers and the adjusted risk of experiencing an admission were increased for cases compared with controls. Specifically, the risk of admission for any cardiovascular reason—cardiac events, cerebral events, acute myocardial infarction, thromboembolic events, and atherosclerotic events—was increased. These findings are in agreement with our finding of increased late cardiovascular mortality for arthroplasty patients.

A major strength of our study is the large-scale population-based cohort with the longest follow-up (21 years) of total hip

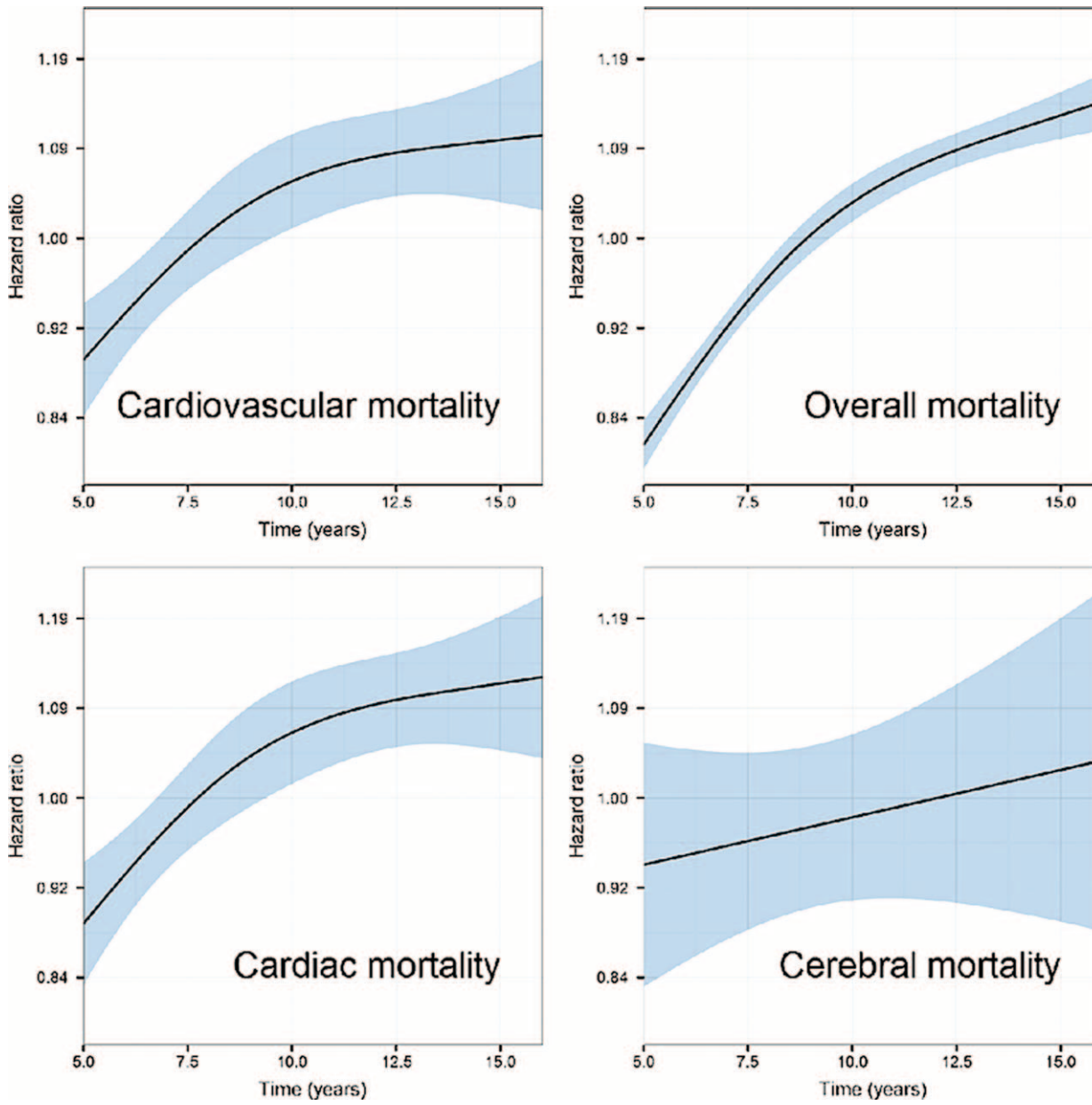

FIGURE 1. Hazard ratio for total hip replacement patients compared with controls. The hazard increases over time; the arthroplasty group exhibits at baseline, 5 y, a hazard lower than the controls. It then crosses over between 8 and 9 y, thereafter the hazard is greater for both the cardiovascular and the overall mortality.

arthroplasty patients ever published on a national level. Another strength is the increased relative risk among patients despite both self-selection and surgeon selection bias; in other words, medically unfit patients will be less inclined for surgery. This is also reflected in our baseline data where the Charlson comorbidities were more prevalent among controls than cases.

A paper by McMinn et al[29] investigating mortality and revision rates following hip arthroplasty raised a debate regarding the importance of residual confounding and its role in the interpretation of register-based research results.[30] Some confounders might not be measured or even measurable; some might be treated too simplistically. We believe that the residual confounding in our study is considerably smaller than in many previous studies since socioeconomic factors are accounted for, at least to some extent.[17,29]

To the best of our knowledge, the analysis of the risk of admission to inpatient care among hip arthroplasty patients and controls is the first of its kind. The Swedish NPR that is the source of our data is considered an instrument with high validity and reliability,[20] which gives us the unique opportunity to analyze the underlying causes of admissions to hospital care in a nationwide cohort of arthroplasty patients and control individuals.

The major limitation to this study is a lack of adjustment for obesity and smoking. Obesity increases the risk of developing osteoarthritis, even though the relationship is weaker for

TABLE 4. Relative Risk (RR) of Admissions to Inpatient Hospital Care for Cardiovascular Reasons

Type of Admission	Avg. Adm. (SD)	RR	2.5% to 97.5%
Cardiovascular			
Control	0.25 (±0.82)	1.00	Ref
Arthroplasty	0.29 (±0.87)	1.13	1.10–1.16
Cardiac			
Control	0.16 (±0.70)	1.00	Ref
Arthroplasty	0.19 (±0.74)	1.12	1.08–1.15
Cerebral			
Control	0.09 (±0.41)	1.00	Ref
Arthroplasty	0.11 (±0.45)	1.15	1.11–1.20
Acute myocardial infarction			
Control	0.12 (±0.55)	1.00	Ref
Arthroplasty	0.14 (±0.58)	1.11	1.07–1.15
Thromboembolic events			
Control	0.09 (±0.41)	1.00	Ref
Arthroplasty	0.11 (±0.45)	1.15	1.11–1.20
Atherosclerotic events			
Control	0.02 (±0.27)	1.00	Ref
Arthroplasty	0.03 (±0.27)	1.13	1.04–1.22

Adjusted for gender, age, and Charlson index score.
SD = standard deviation.

hip osteoarthritis than for knee osteoarthritis. Obesity also increases the risk of cardiovascular disease. Therefore, one could perhaps expect a slight overrepresentation of cardiovascular morbidity among patients who have undergone surgery for hip osteoarthritis compared with controls. Even though there are ICD codes for obesity, these are rarely used and therefore unreliable, thus the question of under-diagnosed obesity remains a limitation of our study. Smoking increases the risk of cardiovascular disease and there are no nationwide data on smoking habits. We therefore used lung cancer as a proxy for comparing smoking in our cohorts, but found no support for increased smoking habits within the arthroplasty group.

Furthermore, the increased relative risk of cardiovascular mortality and morbidity could be mediated through nonsteroidal anti-inflammatory drugs (NSAID). Patients with hip osteoarthritis may often have had treatment with NSAIDs, both pre and postoperatively, and this class of drugs is known to increase the risk of cardiovascular disease.[31,32] The overrepresentation of cardiovascular morbidity in the arthroplasty group could thus be explained by a higher intake of NSAIDs, a factor not possible to control for.

Vascular calcification follows a pathological sequence of events that has similarities to the physiological process of osteogenesis.[33] The receptor activator of nuclear factor κ B (RANK) is a member of the tumor necrosis factor receptor. It is the receptor for the RANK-ligand (RANKL) and part of the RANK/RANKL/osteoprotegerin (OPG) signaling pathway that regulates osteoclast differentiation and activation.[34] A disturbance in the RANK pathway can raise calcification in blood vessels.[35] There is increasing evidence to suggest that both osteopenia and vascular calcification may be linked.[34] Although it is established that the RANKL/OPG signaling pathway is central to the processes regulating bone turnover in a wide variety of medical conditions, there is now a strong clinical association between coronary disease and serum OPG/RANKL levels.[36,37] Therefore, RANKL/OPG are recognized as having equal importance in arterial calcification and osteolysis in bone.[34] In addition to associations of cardiovascular diseases with bone and joint conditions, it is possible that the orthopedic implant in itself can cause local and systemic inflammation. The long-term bone remodeling and local osteopenia[38] and osteolysis[12] around the implants used in total hip arthroplasty may thus activate the RANK/RANKL/OPG pathway. Inflammation associated with the hip implant would probably need an incubation period of several years before the onset of clinical manifestations, mainly affecting long-term survival. While we chose 5 years as the starting point, the data suggest that it takes at least 7 years before an increased risk of mortality is observed. When discussing our finding, perhaps possible increased inflammatory activity in patients with osteoarthritis rather than the performed total hip arthroplasty could explain the increased cardiovascular mortality in this group compared with controls.[39]

CONCLUSIONS

We show that patients with surgically treated osteoarthritis of the hip have an increased risk of cardiovascular morbidity and mortality many years after the operation when compared with control individuals matched for age, sex, and residence. This association remains statistically significant after adjustment for comorbidities. This observation may be indicative of common disease pathways, and one of those could be enhanced local or systemic inflammatory activity.

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